REMARKS

By this amendment claims 1-5, 7, 9 and 17 are amended; claims 1-25 are pending. An introductory article was added to the amended claims 1-5 and 7; typographic errors were corrected in claims 9 and 17. Support for the claim amendments is found in the previous claim set and in the specification as filed, for example, in the original claims. No issue of new matter arises. Entry of the amendment and reconsideration and withdrawal of all pending rejections in each of the multiple parts thereof are respectfully requested.

Interview Acknowledged

Applicants express their gratitude for the courtesies extended their representative in the March 17, 2008 interview a summary of the substance of which is included in the following remarks.

Rejection Under 35 USC §112, second paragraph withdrawn

Applicants gratefully acknowledge that the rejection under 35 USC §112, 2nd paragraph has been withdrawn.

Rejection Under 35 USC §101

Claims 1-8 were again rejected and claims 9-25 were newly rejected under 35 USC §101 as allegedly lacking patentable utility. Applicants respectfully traverse this rejection. In the March 17, 2008 interview, the Examiner indicated several means for addressing the 35 USC §101, utility rejection. Markers for human disease were deemed an issue as were correlative data between the inventive model and human disease.

The Office Action at page 3, first paragraph, indicated that Applicants' earlier argument was not persuasive. The remainder of page 3 discusses credible, specific and substantial utility.

Page 4 then continues with the Examiner's assertion of what the utility should be, irrespective of the application and Applicants' earlier traversals, for example, the reference to: "nothing in the art indicates that any of the characteristics exhibited by the mice (apoptotic lymphocytes and reduced SOD activity and reduced glutathione activity in the brain) are symptoms of Alzheimer's disease. It is noted at this point that the art teaches that Alzheimer's patients exhibit an increase in SOD and glutathione reductase activity." Applicants respectfully

note that despite the Examiner's assertion, not supported by reference to evidentiary data, the art also teaches the opposite. For example, "Scientists have proposed that elevated levels of one form of glutathione, the enzyme glutathione reductase, may serve as a predictor of longevity.[24,25] Falling levels of glutathione are associated with diseases such as AIDS, respiratory diseases and infection, osteoarthritis, **Alzheimer's**, and even aging itself.[26-33] Conversely, increased levels of glutathione are associated with improvements in these conditions."[1] Emphasis added. Applicants further respectfully assert that the apoptotic lymphocytes have utility as a model cell. Accordingly, requiring data to support lymphocytic activities in humans (without transgenically produced multimutated cells) is not proper.

One common feature free of controversy is the free radical (oxidative) stress associated with both the model and Alzheimer's disease. See for example the specification Example 8 (cited by the Examiner): "The deficiency in the mechanisms for protection against free radicals was also revealed in patients suffering from Alzheimer's disease, thus confirming the relevance of this animal model." Applicants' respectfully request an affidavit under 37 CFR 104(d)(2) that

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[1] 24. Klapcinska B, Derejczyk J, Wieczorowska-Tobis K, et al. Antioxidant defense in centenarians (a preliminary study). Acta Biochim Pol. 2000;47(2):281-92.

25. Andersen HR, Jeune B, Nybo H, et al. Low activity of superoxide dismutase and high activity of glutathione reductase in erythrocytes from centenarians. Age Ageing. 1998 Sep;27(5):643-8.

26. Micke P, Beeh KM, Buhl R. Effects of long-term supplementation with whey proteins on plasma glutathione levels of HIV-infected patients. Eur J Nutr. 2002 Feb;41(1):12-8.

27. Micke P, Beeh KM, Schlaak JF, Buhl R. Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients. Eur J Clin Invest. 2001 Feb;31(2):171-8.

28. Bishop C, Hudson VM, Hilton SC, Wilde C. A pilot study of the effect of inhaled buffered reduced glutathione on the clinical status of patients with cystic fibrosis. Chest. 2005 Jan;127(1):308-17.

29. Carlo MD, Jr., Loeser RF. Increased oxidative stress with aging reduces chondrocyte survival: correlation with intracellular glutathione levels. Arthritis Rheum. 2003 Dec;48(12):3419-30.

30. Cho CG, Kim HJ, Chung SW, et al. Modulation of glutathione and thioredoxin systems by calorie restriction during the aging process. Exp Gerontol. 2003 May;38(5):539-48.

31. Junqueira VB, Barros SB, Chan SS, et al. Aging and oxidative stress. Mol Aspects Med. 2004 Feb;25(1-2):5-16.

32. Lothian B, Grey V, Kimoff RJ, Lands LC. Treatment of obstructive airway disease with a cysteine donor protein supplement: a case report. Chest. 2000 Mar;117(3):914-6.

33. Vina J, Lloret A, Orti R, Alonso D. Molecular bases of the treatment of Alzheimer's disease with antioxidants: prevention of oxidative stress. Mol Aspects Med. 2004 Feb;25(1-2):117-23.

explains the Examiner's basis and rationale to enable a formal response to this aspect of the rejection.

The Examiner concludes: "The claimed animals lack substantial utility because further research is required in demonstrating that apoptotic lymphocytes and reduced SOD activity and reduced glutathione reductase activity in the brain are related to Alzheimer's disease. Subsequently, the use of mice as a model of AD and its use in screen for treatment drugs is not readily apparent."

Contrary to this assertion, the Office Action has not rebutted with any evidence of substance the teachings of the application. For example, see page 6, last paragraph: "Thus, the results described in the examples demonstrate that the transgenic mouse expressing the multimutated PS1 develops cellular impairments which are found in Alzheimer's disease and, in particular, exhibits sensitivity to apoptosis." See also, page 7, second paragraph: "Furthermore, the impairments of the metabolism of calcium and of free radicals which are observed very clearly in this model are similar to the increase in the latent period for the calcium response and the oxidative stress which are observed with Alzheimer's patients (Eckert et al., 1997 and 1998) which reinforces the relevance of this model." The Office Action ignores these teachings with only conclusory statements and without any basis for deeming the teachings in the specification as without merit. The Examiner is accordingly respectfully requested to provide supporting affidavit evidence under 37 CFR 104(d)(2) so that Applicants may properly traverse this aspect of the rejection.

At page 4, second paragraph, fourth sentence, the Office Action observes that blood cells are not structurally and functionally the same as neural cells. Applicants concur that there are differences. However, there are also similarities. Applicants have shown that the lymphocytes of the transgenic animals express the transgene (by virtue of a ubiquitous promoter). See, for example, the sentence bridging pages 6 and 7.

But then, at the next two sentences of this paragraph, the Office Action is clear in the intent to dismiss Applicants utility and substitute a utility with a rationale chosen by the Office: "while the mice described in the specification exhibit apoptotic lymphocytes, it is not clear what disease or disorder apoptotic lymphocytes is a symptom of. As such, the use of the claimed animals as a model of apoptotic lymphocytes is not readily apparent." Applicants have suggested a different

utility and supported that utility with the specification teachings and other evidence. It is not proper for the Office to select another utility as the utility upon which to base a rejection. Only one utility is required under 35 USC §101.

Applicants gratefully acknowledge the clarification provided by the Examiner with respect to *Lilly*. Though this explanation is not unambiguous, Applicants respond according to their understanding. The Office Action indicates: "In response [to the request for a more thorough explanation], while the specification clearly indicates "what is" the phenotype of the claimed animals: apoptotic lymphocytes and reduced SOD activity and reduced glutathione reductase activity in the brain, neither the specification not the art provide any guidance as to what relationship these phenotypes have with any disease. . . . The specification asserts that these that these phenotypes are characteristic of Alzheimer's disease (specification, pages 5-6), however, nothing in the art indicates that the characteristics exhibited by the mice described in the Examples of the specification are characteristics of Alzheimer's disease. . . The claimed animal lacks specific utility because the specification's teaching of mutated presenilin and apoptotic lymphocytes and reduced SOD activity and reduced glutathione reductase activity implies that the claimed mice is a model of an undisclosed disease. The claimed model lacks substantial utility because further research is required to determine what this undisclosed disease is."

Applicants respectfully submit that the specification clearly indicates a specific utility, a utility stated rather than implied. See for example, the sentence bridging pages 5 and 6: "it corresponds to a practical model which is representative of the phenomena of cell death in AD." This is one utility clearly stated. The Office cannot properly base a rejection based on assignment of some other utility deemed "implied". Only one utility is required under 35 USC §101. Clearly this requirement is met by the instant specification. Applicants are not required to show that an invention meets any utility chosen by the Office.

At page 6, lines 3 and 4, the Office Action indicates a failure to consider teachings of the application: "it is unclear what use apoptotic lymphocytes have." The apoptotic lymphocytes are a renewable peripheral tissue. The specification, e.g., at page 6, indicates a use for renewable peripheral tissue: "Indeed this model exhibits symptoms associated with AD including in particular apoptosis of the cells and oxidative stress and **makes it possible, in addition, to measure these symptoms in the cells of renewable peripheral tissues.**" Emphasis added.

Thus at least one use is clear. Reconsideration and withdrawal of this rejection are respectfully requested.

Yes the Office Action notes that other evidence might have been presented. However, nothing in the statutes prescribes any specific types of experiment. The requirements of 35 USC §101 are clearly met by the specification. The specification at page 6, last paragraph, teaches: "the examples demonstrate that the transgenic mouse expressing the multimutated PS1 develops cellular impairments which are found in Alzheimer's disease and, in particular, exhibits increased sensitivity to apoptosis." This utility is credible, specific and substantial. Applicants respectfully submit that withdrawal of this rejection is proper.

Applicants gratefully acknowledge the Examiner's agreement at page 6, penultimate paragraph, that the claim is not required to recite utility.

At page 7, the Office Action continues to deny that anything in the art teaches association with SOD and glutathione reductase. Since this assertion has been shown to be false [see page 6 above], reconsideration and withdrawal of this rejection are respectfully requested.

In the paragraph bridging pages 7 and 8, the Office Action appears to require anticipation to prove utility. The office Action has set a legal standard that the art has to provide the utility of what is novel. Applicants respectfully submit that in some cases the novelty itself will require that at least some basis of the utility be in the application disclosure. Nevertheless, in this circumstance the art does provide some basis. For example, whether one accepts the teachings as prior art or as part of the specification, utility is clearly supported in the specification for example at page 2: "Mutations in these genes have been demonstrated to induce an overproduction of αβ especially of the long form αβ42, and to the early appearance of the pathology and symptoms which are similar to those of sporadic forms of AD." Utility of the present invention is further evidenced by this teaching. Reconsideration and withdrawal of this rejection are respectfully requested.

At page 8, the Office Action apparently sums up the first 2 paragraphs with the following two sentences: "In response, as discussed above, lymphocytes are not models of brain cells. As such, this asserted use is not persuasive." Once again the Office is assuming for itself that the Office, not Applicant determines a utility upon which a rejection can be based. Only one utility is required under 35 USC §101. Applicants have not asserted that peripheral tissue cells are

models of any particular cell type, for example, a neuronal cell. Applicants have disclosed a utility of a lymphocyte as a peripheral tissue that has some characteristics of cells associated with neurodegenerative disease associated with oxidative stress. Evidence tying such stress to AD is uncontroverted. Thus utility as required under 35 USC §101 is clear. Reconsideration and withdrawal of this rejection are respectfully requested.

The Examiner states at page 8, last 2 lines, that "since no copy of Chui was provided, the Examiner cannot comment on the publication. Nonetheless, while Applicant refers to Chui who indicate [isn't the Examiner commenting here?] that transgenic models exhibit apoptosis without exhibiting any plaque formation, [Applicants' representative cannot confirm or deny this as the Examiner has not indicated where in Chui this teaching may be] it is noted that nothing in the specification indicates that the claimed animals exhibit apoptosis in the brain." Applicants stand by the assertion that Chui shows a relationship between apoptosis at the level of the neurons and AD. Applicants do not believe that Chui's failure to see plaque formation as asserted by the Examiner is necessary to this discussion. Applicants respectfully submit that a model is a model and not a perfect copy or duplicate. Example 7 for example demonstrates Ca metabolism activity that had been previously been demonstrated in lymphocytes from AD patients. At least this similarity is present in the model and further demonstrates utility of the claimed invention. Nowhere in the statutes can be found any code that requires a showing of apoptosis in the brain. The code is not specific to any particular evidence required. Specific utility is shown with other evidence. Hence this rejection should be withdrawn.

In the closing paragraph of this rejection (page 9, last paragraph), the Office Action reiterates the premise that peripheral tissues are not models of neurons. But neurons are cells as are lymphocytes. Thus they can be expected to serve as models of shared cellular function. The conclusion: "it cannot be extrapolated that apoptotic lymphocytes are models of Alzheimer's" is not fully supported by the simple premise that lymphocytic cells are not models of neuronal cells. An affidavit under 37 CFR 104(d)(2) is respectfully requested to permit Applicants formal response.

Applicants reiterate that utility that is specific substantial and credible is supported in the specification. For example please see pages 5-7.

The animal model according to the invention is very advantageous because it corresponds to a practical model which is representative of the phenomena of cell death in AD. Indeed, this model exhibits symptoms associates with AD including in particular apoptosis of the cells and oxidative stress and makes it possible, in addition, to measure these symptoms in the cells of renewable peripheral tissues. It should be noted that oxidative stress also manifests itself in the brain of these animals. Renewable peripheral tissues should be understood to mean any tissue exhibiting a renewal of these cells over time. By way of example of renewable peripheral tissue, there may be mentioned the spleen, the liver, blood and the like. Preferably, the apoptotic phenomenon is measured in blood cells and still more preferably in the lymphocytes. Among the lymphocytes, the T lymphocytes are preferred for the invention.

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Furthermore, the impairments of the metabolism of calcium and of the free radicals which are observed very clearly in this model are similar to the increase in the latent period for the calcium response and the oxidative stress which are observed with Alzheimer patients (Eckert et al., 1997 and 1998), which reinforces the relevance of this model.

No assertion in the Office Action discredits Eckert et al. Accordingly, the associations of the present invention to the art teachings are unchallenged and therefore should properly be deemed credible.

In view of the above, it is now clear that the rejection under 35 USC §101 is clearly improper. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejections Under 35 U.S.C. §112

Enablement

Claims 1-25 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection. A first aspect of the rejection is laid out on page 10 through page 12. This basis of rejection relies on the continued maintenance of the utility rejection. That rejection having clearly been shown improper in the discussion above, at least this aspect of the rejection is properly withdrawn. Other bases for rejections are discussed below.

At page 12, the Examiner comments on the reasoning of this aspect of the rejection that essentially relies on disbelief of an evidentiary document. A declaration was filed wherein Applicants declared that they each believed the statements of the specification to be true. Penalties under 18 USC §1001 are specifically acknowledged. Accordingly, citation to the specification is no mere assertion. It must be treated as evidence. In the absence of evidence to clearly show that the specification is untrue, the statements in the specification must be considered evidence, not mere assertion by an attorney. The rejection that ignores the deference to be granted the specification accordingly is clearly improper. "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. Cf. *In re Gazave*, 379 F.2d 973, 54 CCPA 1524 (1967); *In re Chilowsky*, 229 F.2d 457, 43 CCPA 775 (1956). The Examples clearly teach how to use peripheral tissue of the transgenic organism as a model for cell activities associated with Alzheimer's disease. In the absence of overwhelming contradictory evidence this evidence is properly accepted by the Office. Reconsideration and withdrawal of this rejection are respectfully requested.

Beginning at the last paragraph of page 12, another basis of rejection is based on speculation outside the claimed subject matter. The Office Action asserts: "Rather, to make the wide variety of mammalian species and transgene constructs such that a particular phenotype is exhibited is undue experimentation, as the art teaches that there is unpredictably in arriving at the appropriate combinations of transgenes and species of host animal." First Applicants did not claim making a "wide variety". Seeing that claim 21 is included in this rejection, perhaps the articles ("the" and "a") included in the present amendment have obviated this rejection.

However if this is not the case, Applicants respectfully assert that they have not claimed a plurality of animals in any claim. The production of any one transgenic species cannot properly be considered to require "undue" experimentation or effort in comparison to production of the wide variety asserted as being undue by the Office Action. The Examiner, at page 13, lines 6 and 5 from bottom, continues this faulty reasoning with the asserted basis for rejection: "it would be undue experimentation to find the appropriate set of transgene constructs for each mammal encompassed by the claims such that the claimed invention could be practiced." The Office

Action has again misread the claims. Nowhere do the claims require the every mammalian species be transgenically altered in order to practice the claimed invention. In fact making only one animal would be deemed an infringing act. While filling an ark with various species might be considered an undue task, producing a single animal as presently claimed does not rise to this level. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The Office Action asserts: "A search in the art has not indicated that there is a relationship between presenilin, apoptotic lymphocytes and Alzheimer's disease." Applicants respectfully request that the Examiner explain why this raises a requirement for undue experimentation.

With respect to Auerbach the Examiner asserts: "Thus, an artisan would be required to make a wide variety of transgenic non-human animals comprising transgene constructs that express a multimutated PS1, wherein said non-human mammal exhibits apoptotic lymphocytes, in order to identify which combination of transgene construct and mammalian specie would result in apoptotic lymphocytes." Applicants reiterate that nothing in any claim requires "a wide variety of transgenic non-human animals". The proper consideration for enablement is each embodiment not the full gamut of embodiments. Practicing the invention is achieved by practicing any single claimed embodiment. One is not required to practice every conceivable embodiment within the scope of a claim to be liable for infringement.

In *Wands*, a seminal case with respect to enablement rejections, millions of molecules were featured, hundreds of thousands were collected, but only a very small fraction met the claim limitations. The variability of amino acid sequence was great and not predictable before the compounds were tested. The specific sequences were not even predictable after results indicating which specific compounds met the claim limitations were determined. Simply measuring binding characteristics (to screen for operative embodiments) does not provide sequence information. (Also in *Wands*, many of the molecules in fact a large majority produced were never tested for binding.) No presumption was made that failure to test each of the millions of compounds produced was evidence supporting a requirement for undue experimentation. Rather the *Wands* guidance clearly teaches that undue experimentation relates to practicing an additional or the next embodiment, clearly not a requirement that all must be tested. Accordingly, *Wands* makes it quite clear that breadth of scope and the possibility or even

certainty of inoperative embodiments cannot constitute a proper basis for rejection. See *Wands*, 8 USPQ2d 1400. Reconsideration and withdrawal of this rejection are respectfully requested.

In the Office Action at the paragraph bridging pages 15 and 16, the phrase "the specification does not teach" and the phrase "Nothing in the specification teaches" appear. Applicants take this to mean that hard evidence was not found in the specification. The Office Action provides no evidence that renewable tissues from the same germ line that contains the always on promoter and gene for multimutated presenilin would not behave as other cells with similar genetic makeup. Indeed as Applicants noted previously some renewable tissues clearly will not have apoptotic capability. A nucleus is required for this, but the skilled artisan would have understood such limitations. These and other possible inoperative embodiments are tolerated in the law. See above. Reconsideration and withdrawal of this rejection are respectfully requested.

Moreover, the approach of this rejection (also including claim 3[2] that is restricted to T-lymphocytes in its purview) indicates that even if data were present in the application for other renewable tissues, this rejection would still be maintained. However, Applicants respectfully submit that since there is no evidentiary basis that other renewable tissues would not behave in a manner similar to their genetic make-up, the evidence in the specification and knowledge in the art are compulsive argument that upon reconsideration, withdrawal of this rejection is proper.

In the paragraph beginning on page 17, the Office Action discounts the evidence in the specification that clearly supports association with Alzheimer's disease and again repeats an unsubstantiated claim that phenotypes of Example 8 "are not indicative that the mice have any symptoms of Alzheimer's disease." The Office Action ignores clear evidence discussed in Examples 7 and 8 and has not provide evidence or argument to prove false the closing statement of Example 8 in the specification at page 29, lines 16-20: "The deficiency in the mechanisms for protection against free radicals was also revealed in patients suffering from Alzheimer's disease, thus confirming the relevance of this animal model." Once again to enable a proper response,

[2] 3. The transgenic animal according to claim 2, characterized in that it allows an apoptotic phenomenon to be detected in its **T lymphocytes**. Emphasis added.

Applicants respectfully request a Rule 104(d)(2) affidavit to support the Examiner's allegations based on personal knowledge.

Finally, in the last sentence of page 17, the Office Action places enablement requirements clearly beyond the scope of the instant claims. "As such, the use of the mice with regard to apoptotic lymphocytes to treat Alzheimer's disease is not readily apparent." Applicants respectfully submit that they have not claimed use of mice to treat Alzheimer's disease. If this rejection is to be maintained, an affidavit under 37 CFR 104(d)(2) is respectfully requested so that Applicants might be able to proper traverse this aspect of the rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

In the Examiner's response at page 18, the Examiner again reiterates the old impossible standard. If it is not novel, then since the art does not teach the invention, it is not enabled.[3] Applicants believe that these bases for rejection have been obviated by discussion above.

Since no experimentation of undue nature has been shown to be required, reconsideration and withdrawal of this rejection is deemed proper.

Indefiniteness

Claims 1-5 and 7 were rejected as allegedly indefinite because they did not begin with an article. These claims are amended in accordance with the Examiner's requirement. Reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

Entry of the amendment is proper under 37 C.F.R. §1.116 because the claim amendments a) place the application in condition for allowance; b) do not raise new issues requiring further search and/or consideration; c) comply with a suggestion made in the Office Action; and/or d) place the application in better condition for appeal should an appeal be necessary.

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance and request prompt issuance of a Notice of Allowance. Should the Examiner wish to suggest additional changes that might put the

[3] "In response, while Applicant indicates that the lymphocytes can be used as a model for Alzheimer's disease, an artisan cannot use apoptotic lymphocytes as a model of Alzheimer's disease because a) the art does not teach that apoptotic lymphocytes are a symptom of Alzheimer's disease and b) lymphocytes are not models of neurons." Last sentence, page 18, first paragraph.

application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

Fees

The Commissioner is hereby authorized to charge any fee required for added claims and any additional fees that may be needed to Deposit Account No. 18-1982.

Respectfully submitted,

Dated: June 18, 2008

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